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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of James T. English, et al. Art Unit 1639
Serial No. 09/829,549
Filed April 10, 2001
Confirmation No. 8198
For PHAGE DISPLAY SELECTION OF ANTI FUNGAL PEPTIDES
Examiner Teresa D. Wessendorf

AMENDED APPEAL BRIEF

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September 25, 2006

AMENDED APPEAL BRIEF

This is an appeal from the final rejection of the claims of the above-referenced application made in the Office action dated July 25, 2005. A Notice of Appeal was filed on December 22, 2005.

This Amended Appeal Brief is being submitted in response to the Notification of Non-Compliant Appeal Brief dated August 24, 2006.

I. REAL PARTY IN INTEREST

The real party in interest is The Curators of the University of Missouri, a corporation of the state of Missouri. An assignment of the above-identified application from the inventors to The Curators of the University of Missouri is recorded in the U.S. Patent and Trademark Office at Reel 011962, Frame 0536.

II. RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any pending appeals or interferences which may be related to, directly affect or be affected by, or have a bearing on, the Board's decision in the present appeal.

III. STATUS OF CLAIMS

The following is a statement of the status of all claims:

Claims 1-9: Rejected under 35 U.S.C. §103(a).

Claims 10-31: Cancelled.

Claims 32-51: Rejected under 35 U.S.C. §103(a).

Thus, claims 1-9 and 32-51 stand rejected under 35 U.S.C. §103(a). The rejection of claims 1-9 and 32-51 under 35 U.S.C. §103(a) is being appealed.

IV. STATUS OF AMENDMENTS

No amendments have been filed after the final rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The following summary is a concise explanation of the subject matter defined in each of the independent claims (1, 48, and 49) involved in the appeal, referring to the specification by page and line number.[1] This summary correlates claim elements to specific embodiments, but does not in any manner limit claim interpretation. Rather, the summary is provided only to facilitate the Board's understanding of the subject matter of this appeal.

Phytophthora is a disease-causing organism causing large losses in many agronomically important crop species. Control of these pathogens is particularly difficult, and often requires the treatment of entire fields with biocidal compounds. While such methods are generally effective, increasing concern about the environment and economic costs of such treatments require the need for alternative control methods. The claimed invention provides a solution to this problem: the use of random peptide

[1] Independent claims 1, 48, and 49 (and dependent claims 2-8, 32-40, 45-47, and 50-51) are grouped together for purposes of this appeal. *See* Section VII, *supra*.

display to identify peptides that bind to pathogenic fungi of the genus *Phytophthora* and other pathogenic fungi.[2]

More specifically, the present invention provides a method for identifying non-immunoglobulin peptides having an affinity for the surface of a plant pathogen. The method of independent claim 1, for instance, comprises:

(a) constructing a library of peptides by (i) preparing random oligonucleotides, (ii) inserting said oligonucleotides into a vector that expresses peptides encoded by said random oligonucleotides on its surface and is capable of transfecting a host cell, and (iii) transfecting a host cell with said vector to amplify said vector in an infectious form to create a library of peptides on the surface of said vector;[3]

(b) contacting a vector expressing the peptide library with a target fungus and removing unbound vector;[4]

(c) eluting bound vector from said fungus;[5]

(d) amplifying the bound vector;[6]

(e) sequencing the oligonucleotides contained in said eluted vector;[7]

(f) deducing the amino acid sequence of peptides encoded by said oligonucleotides contained in said eluted vector;[8] and

(g) selecting the non-immunoglobulin peptides for which the amino acid sequence has been deduced.[9]

Independent claim 48 is similar to independent claim 1 and requires that the target fungus be selected from the group consisting of *Phytophthora sojae*,[10]

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[2] *See* Appellants' Specification, page 1, lines 14-15 and 18-21; and page 4, line 34 to page 5, line 4.
[3] *See* Appellants' Specification, page 10, line 5 to page 12, line 7.
[4] *See* Appellants' Specification, page 12, lines 8-24; *see also* page 21, line 25 to page 22, line 15 (Example 3).
[5] *See* Appellants' Specification, page 12, lines 24-28; *see also* page 21, line 25 to page 22, line 15 (Example 3).
[6] *See* Appellants' Specification, page 17, line 29 to page 13, line 9; *see also* page 22, lines 16-28 (Example 4).
[7] *See* Appellants' Specification, page 13, lines 9-16; *see also* page 22, line 29 to page 23, line 19 (Example 5).
[8] *Id.*
[9] *See* Appellants' Specification, page 13, line 17 to page 14, line 9; *see also* page 22, line 29 to page 23, line 19 (Example 5); page 23, line 20 to page 24, line 16 (Example 6); *and* Figs. 2 and 3.
[10] *See* Appellants' Specification, page 20, lines 12-29 (Example 1).

Phytophthora capsici,[11] *Phytophthora palmivora*,[12] *Phytophthora cinnamomi*,[13] and *Phytophthora parasitica*.[14]

Independent claim 49 is similar to independent claim 1 and requires that the library of peptides be (1) an f8-1 peptide library, wherein each peptide of the f8-1 peptide library has a length of 8 amino acids[15] or (2) an f88-4 peptide library, wherein each peptide of the f88-4 peptide library has a length of 15 amino acids[16].

Claim 9, which depends from claims 1 or 48, requires that each of the peptides be the same length, the length being 6 to 15 amino acids.[17]

Practically speaking, the library of peptides can be displayed on a vector such as phage and incubated with fungi of the genus *Phytophthora* to select for binding peptides. As described in Example 3, the f8-1 or the f88-4 phage-displayed peptide library can be incubated with *Phytophthora* zoospores at room temperature with gentle agitation. Bound phage can then be eluted from the multitude of unknown epitopes on the *Phytophthora* zoospores with an elution buffer and purified. As described in Example 5, DNA can be isolated from phage clones that bound to the *Phytophthora* zoospores and sequenced to determine the peptide sequence that the DNA encodes.

After the binding peptides are identified by these steps, they can be assayed to determine their effect on *Phytophthora*. Importantly, the peptides identified in the examples were effective in inducing premature encystment of *Phytophthora* zoospores (see Appellants' Example 6 and Figs. 2 and 3). This is significant because premature encystment results in the disruption of the pathogenicity of the *Phytophthora* species. Thus, the peptides have an antifungal effect. In particular, the fraction of zoospores encysted by the Appellants' selected phage-bearing peptides was two to seven times greater than the fraction encysted by wild-type phage, as described in Example 6.

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[11] *Id.*
[12] *See* Appellants' Specification, page 2, line 12.
[13] *See* Appellants' Specification, page 2, line 33.
[14] *See* Appellants' Specification, page 20, lines 12-29 (Example 1).
[15] *See* Appellants' Specification, page 11, lines 12-14; lines 16-19; and lines 20-27.
[16] *See* Appellants' Specification, page 11, lines 14-16; and page 11, line 28 to page 12, line 8.
[17] *See* Appellants' Specification, page 10, lines 5-7. Dependent claims 9 and 41-44 are grouped together for purposes of this appeal. *See* Section VII, *supra*.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The only issue presented on appeal is whether the subject matter of claims 1-9 and 32-51 satisfy the requirements of 35 U.S.C. §103(a).

VII. GROUPING OF CLAIMS

For purposes of this appeal, claims 1-9 and 32-51 do not stand or fall together. The claims have been divided into two groups: Group I (claims 1-8, 32-40, and 45-51) and Group II (claims 9 and 41-44). The claims of each of Groups I and II are separately and independently patentable for the reasons described in Sections VIII(A)(1-4) and VIII(B)(1-4), *infra*.

VIII. ARGUMENT

A. The Group I Claims

Claim 1 is representative of the Group I claims. It is directed to a method for identification of **non-immunoglobulin** peptides having an affinity for the surface of a fungus. The method comprises (a) constructing a **library of peptides** by (i) preparing random oligonucleotides, (ii) inserting said oligonucleotides into a vector that expresses peptides encoded by said random oligonucleotides on its surface and is capable of transfecting a host cell, and (iii) transfecting a host cell with said vector to amplify said vector in an infectious form to create a library of peptides on the surface of said vector; (b) contacting said vector expressing said peptide library with a target fungus and removing unbound vector; (c) eluting bound vector from said fungus; (d) amplifying said bound vector; (e) sequencing the oligonucleotides contained in said eluted vector; (f) deducing the amino acid sequence of peptides encoded by said oligonucleotides contained in said eluted vector; and (g) selecting the **non-immunoglobulin peptides** for which the amino acid sequence has been deduced.

1. Gough et al.

Gough et al. describe methods for the isolation of antibodies specific for surface-exposed epitopes on certain species of *Phytophthora* to be used for production of immunological probes and single-chain Fv (scFv) antibodies.[18] Gough et al.'s method involves adding germlings and soluble components thereof to maxisorb immunotubes, blocking, and incubating the maxisorb immunotubes with a **phage-displayed antibody library**.[19] The nonbound phage is removed, and the bound phage eluted and amplified in *E. coli*.[20] These steps are repeated, resulting in a discrete population of phage antibody fragments.[21] The diversity of the eluted antibodies is established by *Bst*NI fingerprinting, and DNA encoding for selected single-chain Fv antibodies is amplified by PCR, digested with restriction endonucleases, and ligated into a vector to produce scFv fusion proteins.[22] The scFv fusion proteins are then used to recognize external epitopes of *Phytophthora*.[23]

Because many of the fungi used to asses the binding of the isolated single-chain Fv antibodies did not produce germlings that adhered to plastic surfaces, the antibodies isolated by Gough et al. had to be tested for their binding to mycelial homogenates.[24] According to Gough et al., however, this assay could not be performed with phage-displayed single-chain Fv's because the phage-displayed form of the antibodies exhibited high background binding to the mycelial homogenates, which necessitated the production of soluble single-chain Fv's.[25] Unfortunately, Gough et al. were also unable to produce detectable amounts of soluble single-chain Fv antibodies from the DNA sequences encoding the selected antibodies.[26] Accordingly, the scFv genes had to be subcloned into an expression vector for the production of a fusion protein containing the single-chain Fv protein and a maltose binding protein (MBP).[27]

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[18] Gough et al. at page 98.
[19] *Id.* at page 99.
[20] *Id.*; *see also* pages 101-102.
[21] *Id.*
[22] Gough et al. at pages 98-99; *see also* pages 102-103.
[23] *Id.* at page 100; *see also* pages 103-104.
[24] *Id.* at page 106.
[25] *Id.*
[26] *Id.*
[27] *Id.*

While the methods of Gough et al. were generally effective in identifying antibodies that bind to the surface of *Phytophthora*, Gough et al. admit that their antibodies and others identified to date **have had no effect on *Phytophthora* whatsoever**. Gough et al. still promise, however, that other antibodies to surface epitopes of *Phytophthora* having a pathogenic effect could still be identified:

> The panning of whole pathogens might be expected to yield scFvs that bind to unmodified surface antigens that may be of importance in the infection process. However, preliminary assays, in which sporangia were mixed with soluble MBP-scFv fusion protein and then used to inoculate tomato leaf discs (Niderman et al., 1995), showed no detectable anti-fungal activity for any of the antibodies. Nevertheless, the isolation of other scFvs specifically directed against the native conformation of surface-accessible antigens may well provide new tools to probe and manipulate pathogenicity.[28]

In contrast to the methods of Gough et al., claim 1 requires the use of a library of non-immunoglobulin peptides, not a library of scFv antibody fragments. Because Gough et al. are concerned with the isolation of antibodies for the surface-exposed epitopes on certain *Phytophthora* species to be used for immunological probes, they are using only single-chain Fv antibody fragments on phage in their disclosed phage display methods, and report no problems with the use of such antibody fragments for their objectives. Significantly, therefore, not only does Gough et al. fail to teach or suggest the use of vector-displayed random peptide libraries in their methods, they also fail to teach or suggest the selection of non-immunoglobulin peptides that bind epitopes on the surface of a fungus.[29] Furthermore, the substitution of random peptide libraries for antibody fragment libraries would be unproductive as Gough et al. seek to identify antibodies which can be used in immunological methods, not mere non-immunoglobulin peptides.[30]

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[28] *Id.* at 107.

[29] *See* Appellants' Specification, page 9, lines 16-19 ("A "non-immunoglobulin peptide" means a peptide which is not an immunoglobulin, a recognized region of an immunoglobulin, or contains a region of an immunoglobulin. For example, a single chain variable region of an immunoglobulin would be excluded from this definition.").

[30] In re Gordon, 733 F.2d 900, 221 USPQ2d 1125 (Fed. Cir. 1984); M.P.E.P. §2143.01. As stated by the Federal Circuit, if proposed a modification would render the prior art unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.

In general, the single-chain Fv antibodies utilized in the methods of Gough et al. are far more complex than the simple peptides in the library of claim 1. Single-chain Fv antibodies such as those utilized in the methods of Gough et al. consist of three independent variable regions of amino acids that are constrained in some fashion (e.g., by folding) by the remaining scFv scaffold. Consequently, the three regions can interact with a target in a constrained manner that is complex and difficult to predict. The scFv scaffold itself may also interact with the target in some manner. Stated another way, the active binding portion of the antibody fragment may or may not work by itself upon subsequent isolation, and/or molecular structures and components other than the active binding portion may be responsible for binding epitopes or surface functions on the target independently or in conjunction with the active binding portion.

The random peptide libraries of claim 1 have far greater utility since they simply have some level of affinity to cell surface factors on the target fungus, without the additional ancillary protein sequences involved in the complex aspects of antibody structure and form. That is, the selected non-immunoglobulin peptides of Appellants' claimed invention can work outside of or independently from a phage-antibody framework to provide a more direct interaction with its targets.

A person of skill in the art must ignore the express teachings of Gough et al. to arrive at a non-immunoglobulin approach using simple peptide libraries. Most significantly, Gough et al.'s approach did not work, i.e., it "showed no detectable anti-fungal activity for any of the antibodies," and, at best, they hold out some vague hope for the future but this hope was limited to scFvs and NOT non-immunoglobulin peptides. Thus, a person of skill in the art would not and could not be motivated to substitute a library of peptides for antibodies in the methods of Gough et al. for the selection of non-immunoglobulin peptides.

The Office vaguely asserts that "the suggested teachings of Gough of non-macromolecular species (i.e., fragments) that retain the recognition characteristics of antibodies like small molecule peptides mimics [*sic*], would suggest the claimed peptide."[31] In fact, Gough et al. teaches and emphasizes the use of antibodies and only antibodies, not simply "species that retain the recognition characteristics of antibodies"

[31] Office action mailed July 25, 2005, at page 3.

as asserted by the Office. In sharp contrast, the Appellants' invention functions independently of immunological response (i.e., non-immunoglobulin) and is claimed as such.[32] Just because you happen to have a peptide that binds to an epitope does not mean that it is an "antibody mimic," as the Office is apparently asserting.

Finally, the Office notes that Gough et al. refer to similar strategies that have been applied to the selection of phage displayed peptides that bind to the surface of intact platelets.[33] This reference by Gough et al., however, implies that mere peptides would be inadequate to accomplish the clearly-stated objectives of Gough et al.

2. Kodadek

Kodadek describes methods of isolating small peptides that recognize **specific, known target peptides** (i.e., target peptides the identity and sequence of which are already known) for use in affinity purification. Kodadek's methods involve an elaborate genetic selection scheme to identify certain library encoded peptides having affinity to a single known target peptide (i.e., not a multitude of unknown epitopes such as those on the surface of a fungus).

Briefly, Kodadek's genetic selection scheme involves forming two compatible constructs, one encoding the known target peptide, and the other encoding a library of DNA fragments, and transforming them into *E. coli*.[34] If a library encoded peptide is present in the library that associates with the target peptide, a complex between the library encoded peptide and the target peptide is formed.[35] The complex blocks certain operator regions in *E. coli*, making it resistant to phage infection challenge.[36] Resistant colonies may then be selected, and the library encoded peptides that bind to the target peptide isolated.[37] As one example, Kodadek discloses utilizing as the target peptide a 13-residue sequence from the protease cleavage site of the human insulin-like growth factor I (IGF-I).[38]

In contrast to the Appellants' claimed invention, Kodadek is concerned with the selection of library encoded peptides having affinity to a single, specific, known target

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[32] *See* Appellants' claim 1 *and* Appellants' Specification, page 9, lines 16-19.
[33] Office action mailed July 25, 2005, at page 4.
[34] Kodadek, page 4, paragraph [0042].
[35] *Id.*; *see also* Kodadek, Figure 1.
[36] *Id.*
[37] *Id.*
[38] *Id.* at page 4, paragraph [0039].

peptide, not a surface with a multitude of unknown epitopes such as the surface of a fungus. Kodadek is not contacting his library encoded peptides with anything other than a provided target peptide (e.g., the protease cleavage site of the human insulin-like growth factor I) to identify binding partners to that particular target.

In essence, Kodadek is describing a prokaryotic analog of a conventional two-hybrid system.[39] Two-hybrid systems, in general, are assays for the detection of peptide-peptide interactions and the identification of genes encoding interactive proteins. As demonstrated by a number of references cited by Kodadek, the use of two-hybrid systems for such purposes is well-known in the art.[40] Like Kodadek, the common two-hybrid system typically involves the interaction of peptides in a peptide library with a target peptide. Generally speaking, however, the two-hybrid system is a much more indirect assay as compared to that of Gough et al. Other than the mere fact that peptides in a peptide library happen to be binding to other peptides (e.g., peptide epitopes), there is no apparent reason why one of skill in the art would be motivated to substitute a library of peptides into the methods of Gough et al. based on Kodadek's disclosure, or any other reference that merely describes the interaction of known peptides with a peptide library for that matter.

Furthermore, Kodadek actually **teaches away** from the use of phage display methods to identify library encoded peptides. Specifically, Kodadek suggests the superiority of his elaborate genetic selection scheme, where other methods have failed. In so doing, Kodadek notes that both **random peptides** (used in the present invention) and antibodies (used in Gough et al.) are **inadequate** for his purpose. As such, Kodadek and Gough et al. represent mutually exclusive domains, and, therefore, any suggestion of substitution of the peptides of Kodadek into the methods of Gough et al. would not be feasible. Thus, one skilled in the art would not and could not be motivated to substitute the highly specialized method of Kodadek into the method of Gough et al. without violating the objective of Gough et al. and rendering it unsatisfactory for its intended purpose.[41]

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[39] *See, e.g.*, Kodadek, page 4, paragraphs [0037]-[0040].
[40] *See, e.g.*, Kodadek, page 4, paragraph [0038], and the list of references provided by Kodadek on pages 18-21, paragraphs [0167]-[0321].
[41] *See supra*, note 30.

The Office has asserted that, by describing the disadvantages in the use of antibodies, Kodadek provided the motivation to substitute peptides into the methods of Gough et al. The Office's assertions apparently rest upon Kodadek's disclosure that "advances in the construction of single chain antibody libraries [scFv's] on phage promise to speed up this process."[42] However, in light of the fact that Kodadek discloses various drawbacks to the use of antibodies in binding studies, the quoted language is nothing more than a suggestion that the disadvantages of antibody usage may be minimized by phage display methodology.

More importantly, Kodadek, in addition to describing the disadvantages of antibodies, also discloses similar disadvantages of peptides, stating that "[u]nfortunately, peptides, or peptide epitopes in proteins, are difficult targets for molecular recognition in aqueous solution,"[43] and that early efforts by Kodadek and co-workers to isolate small peptides using phage display methods "***failed completely***."[44]

Unlike the case for antibodies, Kodadek is devoid of any suggestion that the disadvantages of peptide usage disclosed therein are minimized by any means. Instead, after encountering first-hand the limitation and/or failure of antibodies and phage display, Kodadek resorted to his genetic selection scheme described above to identify certain library encoded peptides having affinity to a given target peptide. Kodadek further describes that, in some cases, even the genetically selected library encoded peptides may not possess the desired affinity for the target.[45] In this event, Kodadek describes that conventional phage display methods may be modified by attaching the genetically selected library encoded peptide to the end of a standard phage displayed peptide library to form a "pincer."[46] The affinity of the genetically selected library encoded peptide arm is improved by the addition of the phage displayed peptide library because the library encoded peptide arm and the phage displayed

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[42] Kodadek, page 1, paragraph [0009] (internal citations omitted).
[43] *Id.* at paragraph [0006].
[44] Kodadek, page 4, paragraph [0038]. Appellants respectfully submit that it is the Office, not the Appellants, which has taken Kodadek's disclosure out of context on this point. (*See* Office action mailed July 25, 2005, at pages 6-7). Clearly Kodadek is referring to the failure of phage display as supporting the biases against the use of peptides.
[45] *Id.* at pages 13-14, paragraphs [0125]-[0134].
[46] *Id.* at page 14, paragraph [0132].

random peptide library arm wrap around the target peptide.[47] Kodadek's specialized "pincer" approach thus facilitates identification of peptide-target interaction where the original peptide-epitope interaction (i.e., the library encoded peptide-known target interaction in the genetic selection scheme) is insufficient for stable interaction.[48]

Instead of providing motivation, a close reading of Kodadek clearly indicates that one skilled in the art would actually be guided away from combining the disclosures of Gough et al. and Kodadek. Keeping this standard in mind, it is significant that Kodadek refers to the futile attempts to identify peptide complexes using phage display that, in Kodadek's words, not only failed but "failed completely." Kodadek then goes on to describe his genetic selection scheme designed to be an improved method, in and of itself, to overcome past failures in identifying peptide complexes. It is only after particular, weakly-binding library encoded peptides that bind to the known target peptide are identified by the genetic selection scheme (i.e., on the basis of affinity) that Kodadek coupled them with conventional phage display methods to form a pincer. Thus Kodadek clearly implies (and in some respects states outright) that conventional phage display methods, standing on their own, would not work. Why else would Kodadek go to all the trouble of devising the genetic selection scheme if random peptide phage display alone would be effective?

3. Petrenko et al.

Petrenko et al. describe methods of forming phage-displayed "landscape libraries" having complex surface functions that would be useful, e.g., in nanotechnology applications. According to Petrenko et al., the complex surface functions of phage clones depend on interactions between neighboring groups of display peptides and wild-type peptides.[49] The emergent properties of the phage surface inhere (i.e., are intrinsic) in the entire surface of the phage, not in the display peptides themselves.[50] Stated another way, Petrenko et al. describe modifications to phage such that the phage will display "global properties" across the entire surface of the phage, not only mere localized properties of the particular displayed peptides. As an example, Petrenko

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[47] *Id.* at paragraphs [0132]-[0133]; *see also* Kodadek, Figure 7.
[48] *Id.*
[49] Petrenko et al. at page 797.
[50] *Id.*

et al. suggest as desirable a phage with a high affinity for a metal ion that displays metal complexed on the surface in a specific repeating geometry.[51] Petrenko et al. also specifically disclose experiments where phage clones were selected for the "global property" of chloroform resistance.[52] Petrenko et al. also describe panning phage displayed peptides against a particular known target material. Such targets included dioxin in one experiment and the lectin concanavalin A in another experiment. In both cases, the phage displayed library of peptides was panned against a **single known target** (i.e., not a multitude of unknown targets such as those on the surface of a fungus).

The lack of teaching, suggestion, or motivation in Gough et al. and Kodadek is not remedied by the disclosure of Petrenko et al. Petrenko et al. describe panning phage displayed peptides against, like Kodadek, a **single known target** seeking to identify phage clones that exhibit "global properties" across the entire phage surface (e.g., chloroform resistance), irrespective of the particular peptides of the library. The "global functions" described in Petrenko et al. were a means to select phage clones that were sensitive to chloroform and to demonstrate that chloroform resistance of the phage depended on the global surface properties of the phage. For example, in Petrenko et al., the mosaic phage was up to 10,000 times more sensitive to chloroform than the corresponding non-mosaic phage.[53]

This is in sharp contrast to the methods of Gough et al., where the target was a multitude of unknown surface epitopes presented on the surface of *Phytophthora*, and the authors were seeking to identify specific antibodies that bind to the surface of *Phytophthora*. Therefore, one skilled in the art would not and could not be motivated to modify the methods of Gough et al. according to the methods described in Petrenko et al. as such a modification would fail to achieve the clearly-stated objectives of each reference.[54]

Moreover, at no point in Petrenko et al. and/or Gough et al. is there any discussion, disclosure, or inference about how the localized properties of phage-peptide

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[51] *Id.* at 801.
[52] *Id.* at 789-799.
[53] Petrenko et al. at page 799.
[54] *See supra,* note 30.

interactions provide an advantage over phage-antibody fragments for the isolation of antibodies. It is not enough that the peptide libraries, or specifically Petrenko et al.'s f8-1 peptide library, could be theoretically substituted into the methods of Gough et al.[55]

In contrast to the focus and methods of Petrenko et al., claim 1 is directed to the identification of peptides displayed on the surface of a vector that have a binding affinity for epitopes displayed on the surface of *Phytophthora*. This goal does not necessarily implicate "global functions" that inhere in the entire surface of phage-peptide. In fact, claim 1 does not even require that the peptide library be expressed on phage. Rather, the peptide library is expressed on a vector, and any vector capable of expressing the peptides of the peptide library may be used.[56] Contrary to the Office's assertion otherwise, the mosaic nature of phage-displayed peptides in Petrenko et al. provides neither suggestion nor motivation to substitute peptides for antibody fragments in the method of Gough et al. in order to identify non-immunoglobulin peptides with affinity for surface epitopes of *Phytophthora*.

Finally, the Office asserts that Petrenko et al. extol the "global functions" that inhere in the entire surface landscape of phage-peptide as motivation to substitute peptides for antibody fragments in the method of Gough et al. As stated above, however, the objectives of Petrenko et al. (global functions) and Gough et al. (antibodies) are far too disparate for one skilled in the art to make such a substitution, particularly since such a substitution would render the prior art being modified unsatisfactory for its intended purpose.[57]

4. The Prior Art Provides No Reasonable Expectation of Success

Collectively, and individually, Gough et al., Kodadek and Petrenko et al. fail to disclose a method for the identification of a peptide, immunoglobulin or otherwise, having anti-fungal properties. Gough et al. merely identified immunoglobulin peptides that bind to the surface of *Phytophthora*; Gough et al. **failed** to demonstrate that their scFvs had any antifungal effect and merely expressed some vague hope that **scFvs**

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[55] In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990); M.P.E.P. §2143.01. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination.
[56] *See* Appellants' Specification, page 11, lines 3-19.
[57] *See supra,* note 30.

may ***one day*** "provide new tools to probe and manipulate pathogenicity."[58] Kodadek was not concerned with the identification of peptides having antifungal properties. Instead, Kodadek was concerned with two-hybrid methods and modifications thereto for isolating small peptides that recognize specific, known target peptides for use in affinity purification; significantly, however, Kodadek developed this approach because **the random peptide approach** (used in the present invention) and antibodies (used in Gough et al.) **were inadequate** for his purpose. Petrenko et al. were concerned with forming phage-displayed "landscape libraries" of general applicability and did not suggest any means for identifying antifungal peptides.

Against this backdrop, claim 1 defines a method which has been successfully used to identify non-immunoglobulin peptides which has been demonstrated to yield peptides having antifungal properties. According to the Office, this approach was obvious despite the fact that Gough et al., the only reference cited by the Office relating to antifungal peptides, **failed to identify any peptides having antifungal properties** and Kodadek said the random peptide approach **failed completely**.[59] Somehow, the Office has concluded a person of ordinary skill would have been led to adopt the method of claim 1 with an expectation of success despite the fact that not one of the three references cited by the Office successfully accomplished this and one of them said that prior attempts to use applicants' approach failed completely.[60] Simply stated, the Office's rejection of claim 1 is nothing more and nothing less than an impermissible hindsight rejection, using Appellants' disclosure as a template.[61]

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[58] Gough et al. at page 107.
[59] Kodadek, page 4, paragraph [0038].
[60] Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1207-8, 18 USPQ2d 1016, 1022-23 (Fed. Cir. 1991) *cert. denied*, 502 U.S. 856 (1991).
[61] M.P.E.P. §2141; U.S. v. Adams, 383 U.S. 39 (1965); Panduit Corp. v. Dennison Mfg. Co., 774 F.2d 1082, 227 USPQ 337 (Fed. Cir. 1985), *vacated and remanded on other grounds*, 475 U.S. 809, 106 S.Ct. 1578 (1986), *adhered to on remand*, 810 F.2d 1561, 1 USPQ2d 1593 (Fed. Cir. 1987); W.L. Gore & Assoc., Inc. v. Garlock, Inc., 721 F.2d 1540, 220 U.S.P.Q. 303, 313 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

B. The Group II Claims

Claim 9 is representative of the Group II claims. It depends from claim 1 (or claim 48) and additionally requires that each of the peptides be the same length, the length being 6 to 15 amino acids.[62]

1. Gough et al.

As discussed above, Gough et al. describe methods for the isolation of antibodies specific for surface-exposed epitopes on certain species of *Phytophthora* to be used for production of immunological probes and single-chain Fv (scFv) antibodies.[63] In contrast to the methods of Gough et al., claim 9 requires the use of peptides that are the same length, the length being 6 to 15 amino acids, not scFv antibody fragments.

The single-chain Fv antibodies utilized in the methods of Gough et al. are far more complex than the simple, 6- to 15-mer random peptides required by claim 9. While the Office cites no authority regarding the molecular weight of scFv antibodies, it is the Appellants' understanding that such scFv antibodies generally have a molecular weight of at least about 24,000, with 29,000 to 30,000 being typical. Based on a molecular weight of 24,000 and using an average molecular weight of 137 for the 20 possible amino acids, Gough et al.'s antibody fragments would be about 175 amino acids in length; thus, Gough et al.'s antibody fragments are, at a minimum, 12 times longer than the 6- to 15-mer peptides required by claim 9. In addition, Gough et al.'s single-chain Fv antibodies include ancillary protein sequences that are involved in antibody structure and form, and may not work outside or independent of the complex phage-antibody framework.[64] Thus, not only do Gough et al. fail to teach or suggest the use of peptides in their methods, they also fail to teach or suggest peptides having the same length, the length being 6 to 15 amino acids.

A person of skill in the art must ignore the express teachings of Gough et al. to arrive at peptides having the same length, the length being 6 to 15 amino acids. Most

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[62] The Group II claims are claims 9 and 41-44. Claims 41 and 43 are comparable to claim 9 except that they require the peptides to be 8 amino acids and 15 amino acids in length, respectively. Claims 42 and 44 require the peptide library to be the f8-1 and the f88-4 peptide library, respectively. As described in Appellants' Specification page 11, lines 3-19, the f8-1 peptide library includes random peptides that are 8 amino acids in length and the f88-4 peptide library includes random peptides that are 15 amino acids in length.

[63] *See supra* Section VIII(A)(1).

[64] *See supra* Section VIII(A)(1).

significantly, Gough et al.'s approach "showed no detectable antifungal activity for any of the antibodies," and, at best, they hold out a vague hope for the future limited only to scFv antibodies and not peptides of a specific length.[65]

2. Kodadek

As discussed in detail above, Kodadek is concerned with the selection of library encoded peptides having an affinity to a single, specific, known target peptide, not a surface with a multitude of unknown epitopes such as the surface of a fungus. To accomplish his goals, Kodadek describes modifications to a conventional two-hybrid system. In so doing, Kodadek notes that both **random peptides** (e.g., 6 to 15-mer peptides required by claim 9) and antibodies (used in Gough et al.) are **inadequate** for his purpose. Most significantly, at the time of the present invention Kodadek had already stated that phage display methods were not only ineffective in identifying small peptides, they were a ***complete failure***.[66] Thus, Kodadek **teaches away** from the use of phage display methods to identify library encoded peptides, regardless of length.

3. Petrenko et al.

Petrenko et al., like Kodadek, describe panning phage-displayed peptides against a single known target seeking to identify phage clones that exhibit "global properties" across the entire phage surface. That is, Petrenko et al. describe modifications to phage such that the phage will display "global properties" across the entire surface of phage, not only mere localized properties of the particular displayed peptides.[67] This is in sharp contrast to the methods of Gough et al., where the target was a multitude of unknown surface epitopes presented on the surface of *Phytophthora* and the authors were seeking to identify specific antibodies that bind to the surface of *Phytophthora*.

4. The Prior Art Provides No Reasonable Expectation of Success

At the time of Appellants' invention, Petrenko et al.'s peptide libraries were known in the art, and Gough et al. still selected a phage-antibody library of scFv fragments. Incredibly, the Office has nonetheless concluded that Petrenko et al.'s phage-displayed peptides could be substituted into the methods of Gough et al. The

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[65] *Id. See also* Gough et al. at page 107.
[66] *See supra* Section VIII(A)(2). *See also* Kodadek, page 4, paragraph [0038].
[67] *See supra* Section VIII(A)(3). *See also* Petrenko et al. at page 797.

Office makes this assertion despite the fact that Gough et al.'s method "showed no detectable antifungal activity for any of the antibodies" and Kodadek said it would not work. There is simply ***no reason*** to believe that the substitution of smaller peptides such as those having a length of 6 to 15 amino acids would even work, let alone provide an improvement over the larger scFv antibodies of Gough et al.

IX. CONCLUSION

A *prima facie* case of obviousness has not been established pursuant to 35 U.S.C. § 103(a) based on the combined references of Gough et al., Kodadek, and Petrenko et al. It has not been shown that the cited references would have motivated a person of ordinary skill in the art to make the Appellants' invention, would have provided a reasonable expectation of success, or when considered as a whole, would have suggested all of the requirements of the claimed invention. For these reasons, and for those more fully stated above, Appellants respectfully request the rejections be reversed and claims 1-9 and 32-51 be allowed.

The Commissioner is hereby authorized to charge any additional fees which may be required to Deposit Account No. 19-1345.

Respectfully submitted,

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CLAIMS APPENDIX

1. (previously presented) A method for identification of non-immunoglobulin peptides having an affinity for the surface of a fungus comprising:

(a) constructing a library of peptides by,

(i) preparing random oligonucleotides;

(ii) inserting said oligonucleotides into a vector that expresses peptides encoded by said random oligonucleotides on its surface and is capable of transfecting a host cell;

(iii) transfecting a host cell with said vector to amplify said vector in an infectious form to create a library of peptides on the surface of said vector;

(b) contacting said vector expressing said peptide library with a target fungus and removing unbound vector;

(c) eluting bound vector from said fungus;

(d) amplifying said bound vector;

(e) sequencing the oligonucleotides contained in said eluted vector;

(f) deducing the amino acid sequence of peptides encoded by said oligonucleotides contained in said eluted vector; and

(g) selecting the non-immunoglobulin peptides for which the amino acid sequence has been deduced.

2. (previously presented) The method of any one of claims 1, 48, or 49 further comprising repeating steps (b) through (d) at least once.

3. (previously presented) The method of any one of claims 1, 48, or 49, wherein said vector is a fusion phage vector.

4. (previously presented) The method of any one of claims 1, 48, or 49, wherein said vector is a fusion phage vector selected from the group consisting of type 8,

type 88, type 8+8, type 3, type 33, type 3+3, type 6, type 66, type 6+6, phage T7 and phage 8.

5. (previously presented) The method of any one of claims 1 or 48, wherein the sequence of said random oligonucleotide is GCA GNN (NNN)7 or SEQ ID NO: 1.

6. (previously presented) The method of any one of claims 1, 48, or 49, wherein said peptide is expressed as part of a coat protein of said vector.

7. (original) The method of claim 6, wherein said coat protein is a pIII or a pVIII coat protein.

8. (previously presented) The method of any one of claims 1, 48, or 49, further comprising determining the binding affinity of said peptides to said target fungus.

9. (previously presented) The method of any one of claims 1 or 48, wherein each of said peptides are of the same length, the length being 6 to 15 amino acids.

10-31. (canceled)

32. (previously presented) The method of any one of claims 1 or 49 wherein the target fungus is a plant pathogenic fungus.

33. (previously presented) The method of any one of claims 1 or 49 wherein the target fungus is a member of genus *Phytophthora*.

34. (previously presented) The method of any one of claims 1 or 49 wherein the target fungus is selected from the group consisting of *Phytophthora sojae*, *Phytophthora capsici*, *Phytophthora cactorum*, *Phytophthora palmivora*, *Phytophthora cinnamomi*, *Phytophthora infestans*, and *Phytophthora parasitica*.

35. (previously presented) The method of any one of claims 1 or 49 wherein the target fungus is selected from the group consisting of *Phytophthora sojae*, *Phytophthora capsici*, *Phytophthora palmivora*, *Phytophthora cinnamomi*, and *Phytophthora parasitica*.

36. (previously presented) The method of any one of claims 1 or 49 wherein the target fungus is *Phytophthora sojae* or *Phytophthora capsici*.

37. (previously presented) The method of any one of claims 1, 48, or 49 wherein the vector expressing the peptide library is contacted with the target fungus at different life stages of the target fungus.

38. (previously presented) The method of any one of claims 1, 48, or 49 wherein the vector expressing the peptide library is contacted with the target fungus at oospore life stage or chlamydospore life stage.

39. (previously presented) The method of any one of claims 1, 48, or 49 wherein the vector expressing the peptide library is contacted with the target fungus at zoospore life stage.

40. (previously presented) The method of any one of claims 1, 48, or 49 wherein the vector expressing the peptide library is contacted with the target fungus at germling life stage.

41. (previously presented) The method of any one of claims 1 or 48 wherein each of said peptides are of a same length, the length being 8 amino acids.

42. (previously presented) The method of any one of claims 1 or 48 wherein the peptide library is an f8-1 peptide library.

43. (previously presented) The method of any one of claims 1 or 48 wherein each of said peptides are of a same length, the length being 15 amino acids.

44. (previously presented) The method of any one of claims 1 or 48 wherein the peptide library is an f88-4 peptide library.

45. (previously presented) The method of any one of claims 1, 48, or 49, further comprising repeating steps (b) through (d) at least twice.

46. (previously presented) The method of any one of claims 1, 48, or 49, further comprising repeating steps (b) through (d) at least three times.

47. (previously presented) The method of any one of claims 1, 48, or 49 wherein the bound vector is amplified in an *E. coli*.

48. (previously presented) A method for identification of non-immunoglobulin peptides having an affinity for the surface of a fungus comprising:

(a) constructing a library of peptides by,

(i) preparing random oligonucleotides;

(ii) inserting said oligonucleotides into a vector that expresses peptides encoded by said random oligonucleotides on its surface and is capable of transfecting a host cell;

(iii) transfecting a host cell with said vector to amplify said vector in an infectious form to create a library of peptides on the surface of said vector;

(b) contacting said vector expressing said peptide library with a target fungus and removing unbound vector, wherein the target fungus is selected from the group consisting of *Phytophthora sojae*, *Phytophthora capsici*, *Phytophthora palmivora*, *Phytophthora cinnamomi*, and *Phytophthora parasitica*;

(c) eluting bound vector from said fungus;

(d) amplifying said bound vector;

(e) sequencing the oligonucleotides contained in said eluted vector;

(f) deducing the amino acid sequence of peptides encoded by said oligonucleotides contained in said eluted vector; and

(g) selecting the non-immunoglobulin peptides for which the amino acid sequence has been deduced.

49. (previously presented) A method for identification of non-immunoglobulin peptides having an affinity for the surface of a fungus comprising:

(a) constructing a library of peptides by,

(i) preparing random oligonucleotides;

(ii) inserting said oligonucleotides into a vector that expresses peptides encoded by said random oligonucleotides on its surface and is capable of transfecting a host cell;

(iii) transfecting a host cell with said vector to amplify said vector in an infectious form to create a library of peptides on the surface of said vector;

wherein the library of peptides is (1) an f8-1 peptide library, wherein each peptide of the f8-1 peptide library has a length of 8 amino acids or (2) an f88-4 peptide library, wherein each peptide of the f88-4 peptide library has a length of 15 amino acids;

(b) contacting said vector expressing said peptide library with a target fungus and removing unbound vector;

(c) eluting bound vector from said fungus;

(d) amplifying said bound vector;

(e) sequencing the oligonucleotides contained in said eluted vector;

(f) deducing the amino acid sequence of peptides encoded by said oligonucleotides contained in said eluted vector; and

(g) selecting the non-immunoglobulin peptides for which the amino acid sequence has been deduced.

50. (previously presented) The method of claim 49 wherein the library of peptides is a f8-1 peptide library, wherein each peptide of the f8-1 peptide library has a length of 8 amino acids.

51. (previously presented) The method of claim 49 wherein the library of peptides is a f88-4 peptide library, wherein each peptide of the f88-4 peptide library has a length of 15 amino acids.

EVIDENCE APPENDIX

Not applicable.

RELATED PROCEEDINGS APPENDIX

Not applicable.